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Hyperventilation-Induced Simultaneous Multivessel Coronary Spasm in Patients With Variant Angina: An Echocardiographic and Arteriographic Study

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Left ventricular wall motion abnormalities during an attack of coronary spasm induced by hyperventilation were examined with use of two-dimensional echocardiography in 27 patients with variant angina. Transient abnormal wall motion (asynergy) confined to one coronary artery region was found in 18 of the 27 patients and transient abnormal motion extending over more than one coronary artery region in the remaining 9 patients. Spasm of more than one major coronary artery was demonstrated separately by coronary arteriography during an attack induced by injection of acetylcholine or ergonovine in seven of the nine patients who manifested asynergy in more than one coronary artery region. In one patient, spasm was demonstrated in one major coronary artery, and the other coronary arteries were severely stenosed or occluded organically. In the remaining patient, acetylcholine was not injected into both arteries; however, the attack was sometimes associated with ST segment elevation in the anterior leads and at other times in the inferior leads.

Therefore, simultaneous multivessel coronary spasm seems to have occurred in eight of the nine patients who exhibited asynergy in more than one coronary artery region. The 8 patients with simultaneous multivessel coronary spasm had a higher degree and longer duration of ST segment elevation and a higher incidence of arrhythmias during the attack induced by hyperventilation than did the 19 patients with single vessel coronary spasm, and all of them had no significant organic stenosis.

It is concluded that 1) simultaneous multivessel coronary spasm seems to occur in a sizable proportion (30%) of patients with variant angina and can be detected by two-dimensional echocardiography; and 2) an attack of simultaneous multivessel coronary spasm is associated with more severe and more prolonged myocardial ischemia than that of single vessel coronary spasm and it typically occurs in normal or nearly normal coronary arteries.

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Variant angina is characterized by recurrent attacks of chest pain occurring at rest and associated with ST segment elevation on the electrocardiogram (ECG) (1). It is now established that this syndrome is caused by spasm of a major coronary artery (2–5). The leads in which ST segment elevation occurs are usually the same during each attack in the same patient, indicating that spasm usually appears in the same coronary artery in the same patient. However, in some patients ST segment elevation occurs in the anterior and the inferior leads at different times. In such patients, spasm sometimes occurs in the left anterior descending coronary artery and at other times in the right or a dominant left circumflex coronary artery (6). Indeed, there are several reports (7–11) of spasm in more than one coronary artery (multivessel coronary spasm). However, there have been no systematic studies on simultaneous multivessel coronary spasm. We recently reported (12) that, in patients with variant angina, intracoronary injection of acetylcholine can induce spasm in each susceptible artery separately and that the incidence of multivessel coronary spasm is surprisingly high (76%) in these patients.

Echocardiography has been used clinically to detect and quantify regional wall motion abnormalities of the left ven-

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tricle induced by myocardial ischemia, and it has been shown (13–15) to be more sensitive than the ECG for detecting and quantifying myocardial ischemia. The present study was designed 1) to examine whether two-dimensional echocardiography can detect simultaneous multivessel coronary spasm during the attack in patients with variant angina using coronary arteriography during the attack as the reference standard, and 2) if so, to differentiate the clinical features of simultaneous multivessel coronary spasm from those of single vessel coronary spasm.

Methods

Study patients. Of 48 patients with variant angina who underwent a hyperventilation test, 31 (25 men and 6 women with a mean age of 56 years) in whom an attack of coronary spasm with ST segment elevation on the ECG was induced were entered into the study. No patient had bundle branch block, previous myocardial infarction or evidence of impaired ventricular function at rest as assessed by echocardiography and cardiac catheterization.

Provocation of attacks of coronary spasm. The hyperventilation test was performed in the early morning for provocation of the anginal attack (6:00 AM to 7:30 AM). After a control 12 lead ECG and echocardiogram were recorded, the patients hyperventilated vigorously for 3 to 8 min. The end point of hyperventilation was the appearance of ST segment elevation on the ECG, light-headedness or numbness of the lips and limbs (15,16). This test was performed within 10 days of coronary angiography. Administration of all drugs except nitroglycerin was stopped 2 days before the study; nitroglycerin administration was stopped 2 h before the study. All patients gave written informed consent.

Electrocardiography. A complete 12 lead tracing was obtained at 1 min intervals or more often, and three leads (usually leads III, aVL and V_3 or V_4) were continuously monitored during the test. The appearance of transient ST segment elevation >0.1 mV at 0.08 s after the J point as compared with the control was considered diagnostic of myocardial ischemia caused by spasm. The ischemia was considered to be present in the anterior wall when the changes occurred in leads V_1 to V_4, in the lateral wall when changes occurred in leads I, aVL, V_5 and V_6, and in the inferior wall when changes occurred in leads II, III and aVF.

Echocardiography. Echocardiographic examination was performed with a wide angle phased array system and a 3.5 MHz transducer (SSH 40-A or SSH 60-A, Toshiba). The patients were placed in the slight left decubitus position during the test. A two-dimensional echocardiogram and a simultaneous M-mode tracing in the standard parasternal or subcostal short-axis view of the left ventricle at the level of the papillary muscles were obtained continuously before and after hyperventilation. All images were recorded on videotape (VT-7, Hitachi) for later analysis. The short-axis view

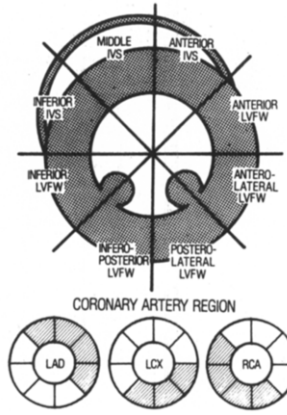

Figure 1. Schematic diagram of short-axis view of the heart divided into eight segments as recommended by the American Society of Echocardiography (17) and of the vascular region of each major coronary artery as indicated by the **shaded area (lower panel).** IVS = interventricular septum; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LVFW = left ventricular free wall; RCA = right coronary artery.

of left ventricle at the level of the papillary muscles, in which areas of the myocardium perfused by all three major coronary arteries can be visualized, was divided into eight segments according to the recommendations of the American Society of Echocardiography (17) (Fig. 1).

Analysis of wall motion. Regional wall motion of these eight segments was classified as normal, hypokinetic, akinetic or dyskinetic on the basis of motion of the endocardial echo with respect to the center of the left ventricular cavity. Special attention was directed to the degree of systolic wall thickening of the myocardium and a segment was defined as akinetic when it had no systolic myocardial thickening even if slight inward endocardial motion was present during systole. The general term asynergy was used to describe any segment graded hypokinetic, akinetic or dyskinetic. For the purpose of this study, akinetic and dyskinetic segments were considered as a single grade. The grade of asynergy was defined by comparing the motion and degree of systolic wall thickening of each segment with those during control conditions before hyperventilation. Wall motion and systolic wall thickening were assessed by two independent observers without knowledge of the ECG during a spontaneous attack or results of coronary arteriography or radionuclide studies; discrepancies were resolved by consensus.

Coronary artery region. The coronary artery region for a single coronary artery was defined as the entire zone of observed asynergy. Because the interventricular septum has

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a dual supply of vessels from the anterior and posterior descending arteries with predominance of the former, the anterior two thirds of the interventricular septum (anterior and midventricular septum) was considered as the area perfused by the left anterior descending artery, and the posterior one third (inferior ventricular septum) as that perfused by the posterior descending artery (18,19). The anterolateral left ventricular free wall is perfused by the diagonal branches of the left anterior descending artery in some cases and by the obtuse marginal branches of the left circumflex artery in other cases. Thus, in the present study ischemia caused by obstruction of the left anterior descending artery was assumed to be the cause of asynergy in any of the segments from the midventricular septum to the anterolateral left ventricular free wall. The left circumflex artery usually supplies the anterolateral and posterolateral left ventricular free wall, and the right coronary artery supplies the inferoposterior and inferior left ventricular free wall and the inferior ventricular septum (20). However, the left circumflex artery and right coronary artery regions overlap considerably depending on the dominance of either the right or the left coronary artery; therefore, the area perfused by the left circumflex artery could not be reliably distinguished from that perfused by the right coronary artery by examining only inferior and lateral asynergy (21). Thus, in the present study, ischemia due to obstruction of the left circumflex artery was assumed to cause asynergy in any of the segments from the anterolateral left ventricular free wall to the inferoposterior left ventricular free wall. Ischemia caused by obstruction of the right coronary artery was assumed to cause asynergy in any of the segments from the posterolateral left ventricular free wall to the inferior ventricular septum (Fig. 1). This procedure established the maximal distribution of akinetic segments for each of the three major coronary arteries, although individual patients seldom had akinesia involving all potential segments.

Adjacent and remote asynergy. It is known that nonischemic muscle adjacent to ischemic or damaged myocardium exhibits mechanical dysfunction. This "adjacent nonischemic asynergy" may in part be the result of a tethering effect and is used to explain the fact that the extent of wall motion abnormalities detected by two-dimensional echocardiography overestimates the ischemic area or infarct size (22–24). In the present study, adjacent asynergy was defined as a hypokinetic segment contiguous with an akinetic or dyskinetic segment. Adjacent asynergy that occurred outside a single arterial region was considered a manifestation of a single arterial event. On the other hand, remote asynergy was defined as a nonadjacent segment that was hypokinetic, akinetic or dyskinetic outside of a single arterial region. Therefore, occurrence of remote asynergy was not considered a manifestation of a single arterial event (21).

Coronary angiography. Coronary angiography was performed in all patients with the Sones technique. Provocation of spasm was performed by the intracoronary injection of acetylcholine into the right and left coronary arteries separately as described in previous reports (12,25,26). Briefly, acetylcholine, 20 to 100 μg, is injected into the right and left coronary arteries to induce spasm of each artery separately. When spasm of one coronary artery was induced with this method, it usually resolved spontaneously within a few minutes. When spasm persisted and hemodynamic instability or prolonged bradycardia developed, nitroglycerin was administered. In four patients, acetylcholine was injected only into the artery predicted to be responsible for the spontaneous attack (the right coronary artery in three patients, the left coronary artery in one). If spasm was not induced by the intracoronary injection of acetylcholine, ergonovine, 0.2 mg, was administered intravenously (four patients). The appearance of total or subtotal occlusion of a major coronary artery associated with ST segment elevation or depression on the ECG or chest pain, or both, was considered to be a manifestation of spasm. After sublingual administration of nitroglycerin, 0.3 mg, the coronary arteriograms were filmed in multiple projection. Significant coronary artery disease was defined as ≥50% luminal diameter narrowing.

Statistics. Data are expressed as the mean value ± SD; the unpaired *t* test was used to compare differences between groups. The chi-square test was used for differences in event frequency between groups using the Yates correction where appropriate. A probability (p) value <0.05 was considered statistically significant.

Results

Of the 31 patients in whom hyperventilation provoked the attack of coronary spasm with ST segment elevation, 4 patients were excluded from the study because they had suboptimal echocardiographic images. Thus, the remaining 27 patients are the subjects of the present study. The clinical, ECG, angiographic and echocardiographic findings of these 27 patients are shown in Table 1.

Analysis of wall motion. Two-dimensional echocardiography revealed that asynergy appeared during the attack of spasm and disappeared after nitroglycerin administration in all 27 patients. Asynergy during the attack was localized within one arterial region reflected by ST segment elevation in 18 patients (11, 5 and 2 patients in the right, left anterior descending and left circumflex coronary artery region, respectively). In the remaining nine patients, asynergy was detected in more than one arterial region (the left anterior descending and right coronary artery regions in eight patients and the left circumflex and right coronary artery regions in one) (Fig. 2). There was a small discrepancy in classifying the wall motion of each segment, but there was complete agreement on judging the presence or absence of

Table 1. Clinical, Electrocardiographic, Coronary Arteriographic and Echocardiographic Data in 27 Patients

Case No.	Age (yr) & Gender	ST Elevation During Spontaneous Attack (ECG leads)	Coronary Arteriographic Findings (% Stenosis after TNG) RCA	LAD	LCx	Site of Spasm	ST Changes During HV Test	Magnitude of ST Elevation (mV)	Duration of ST Elevation (s)	Arrhythmia	Simultaneous Multivessel Spasm During HV Test
Patients Showing Asynergy Within One Coronary Artery Region											
1	57M	Inf	—	—	—	RCA, LCx	II, III, aVF ↑ I, aVL, V_1 to V_5 ↓	0.3	203	No	–
2	43M	Inf	—	—	—	RCA	II, III, aVF ↑ I, aVL ↓	0.2	165	No	–
3	48M	Inf	—	—	—	RCA	II, III, aVF ↑ I, aVL ↓	0.2	155	No	–
4	61M	Inf	90	—	—	RCA	II, III, aVF ↑ I, aVL, V_1 to V_5 ↓	0.1	150	No	–
5	57M	Inf	—	—	75	LCx (EM)	II, III, aVF ↑ aVL, V_5 to V_6 ↓	0.2	60	No	–
6	59M	Inf	75	—	—	RCA	II, III, aVF ↑ I, aVL, V_1 to V_5 ↓	0.4	120	No	–
7	68M	Inf	90	—	—	RCA	II, III, aVF ↑ I, aVL, V_5 to V_6 ↓	0.2	60	No	–
8	56F	Inf	—	—	—	RCA, LAD	II, III, aVF ↑ I, aVL, V_1 to V_4 ↓	0.2	195	SVE	–
9	63F	Inf	50	—	—	RCA	II, III, aVF ↑	0.1	75	No	–
10	68M	Inf	75	75	—	RCA (EM)	II, III, aVF ↑ I, aVL, V_5 to V_6 ↓	0.15	215	No	–
11	57M	Inf	90	—	90	RCA	II, III, aVF ↑	0.1	180	No	–
12	62M	Ant	—	75	—	LAD	V_1 to V_4 ↑	0.15	75	No	–
13	56M	Ant	—	—	—	RCA, LAD	V_1 to V_4 ↑ II, III, aVF ↓	0.9	90	SVE	–
14	70M	Lat	50	—	—	RCA, LCx	I, aVL ↑ II, III, aVF ↓	0.1	60	No	–
15	65M	Ant	—	99	75	RCA, LAD	aVL, V_1 to V_4 ↑ II, III, aVF ↓	1.05	255	VE	–
16	55M	Inf, ant	—	—	—	RCA, LAD (EM)	V_2 to V_5 ↑	0.2	100	No	–
17	51M	Inf	—	—	—	RCA, LCx	II, III, aVF, V_5 to V_6 ↑ $V1_1$ to V_4 ↓	0.5	200	No	–
18	41M	Ant, inf	—	75	—	RCA	I, aVL, V_1 to V_4 ↑ II, III, aVF ↓	1.4	210	VE	–
Patients Showing Asynergy Extending Over More Than One Coronary Artery Region											
19	47M	Ant	100	90	75	LAD	V_1 to V_5 ↑ I, aVL, II, III, aVF ↓	0.65	210	No	–
20	67M	Ant, inf	—	—	—	RCA	II, III, aVF ↑ I, AVL, V_2 to V_6 ↓	1.0	390	SB	+
21	68M	Inf	—	—	—	RCA, LAD	II, III, aVF ↑ I, aVL, V_2 to V_4 ↓	0.25	180	VE	+
22	57M	Inf	—	—	—	RCA, LCX, LAD	II, III, aVF ↓ I, aVL, V_1 to V_6 ↓	1.3	300	VE	+
23	53F	Inf	—	—	—	RCA, LCx (EM)	II, III, aVF ↑ I, aVL, V_5 to V_6 ↓	0.2	285	Couplets of VE	+
24	52F	Inf, ant	—	—	—	RCA, LAD	V_1 to V_4 ↑ II, III, aVF ↓	0.8	360	VT	+
25	61M	Inf, ant	—	—	—	RCA, LAD	V_1 to V_5 ↑ II, III, aVF ↓	0.55	210	VT	+
26	50M	Inf, ant	—	—	—	RCA, LAD	V_2 to V_6, I, aVL and II, III, aVF ↑	1.2	160	VT	+
27	52F	Inf, ant	—	—	—	RCA, LAD	V_1 to V_4, II, III, aVF ↑	0.45	195	VT	+

Ant = anterior; EM = spasm was induced by ergonovine; F = female; HV = hyperventilation; Inf = inferior; LAD = left anterior descending artery; Lat = lateral; LCx = left circumflex artery; M = male; No = no arrhythmias; RCA = right coronary artery; SB = marked sinus bradycardia; SVE = frequent supraventricular extrasystoles; TNG = nitroglycerin; VE = frequent ventricular extrasystoles; VT = ventricular tachycardia; + = occurrence of simultaneous multivessel coronary spasm; – = no occurrence of simultaneous multivessel coronary spasm; ↑ = ST segment elevation; ↓ = ST segment depression; — = <50% stenosis.

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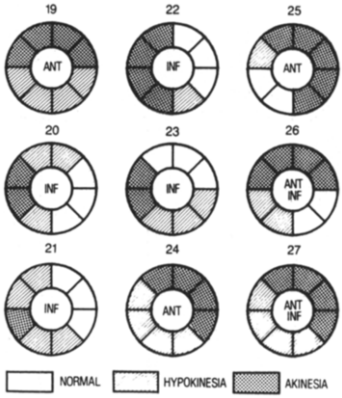

Figure 2. Diagrams showing extent and degree of asynergy of nine patients in whom asynergy was detected in more than one coronary artery region. Normal, hypokinetic and akinetic/dyskinetic segments were determined by two-dimensional echocardiography. The echocardiographic segment model is similar to that of Figure 1. The numbers refer to the case numbers in Table 1. The site of ST segment elevation on the ECG during the attacks induced by hyperventilation is shown in the inner circle. Ant = anterior, Inf = interior.

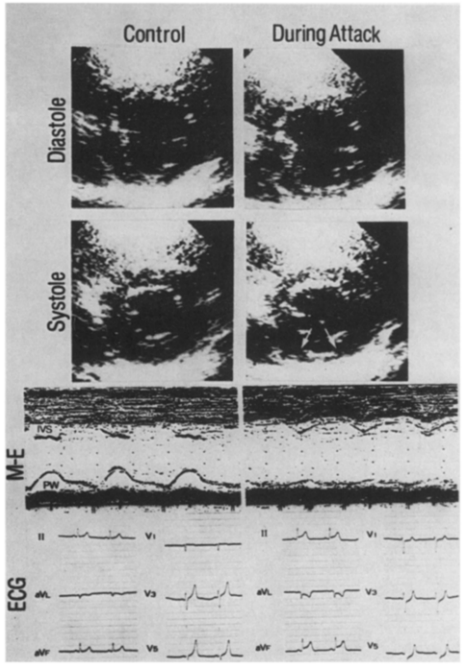

Figure 3. Case 6. Two-dimensional echocardiograms (**top**). M-mode echocardiograms (M-E) (**middle**) and electrocardiograms (ECG) (**bottom**) during control (**left**) and during an attack of coronary spasm (**right**) in a patient who showed asynergy within one coronary artery region. During the attack, the ECG revealed marked ST segment elevation in the inferior leads with ST segment depression in the contralateral leads. Marked reduction of motion and systolic thickening of the posterior wall (PW) appeared with relatively hyperkinetic motion of the interventricular septum (IVS) in the M-mode echocardiogram. The short-axis images of the left ventricle showed no systolic wall thickening in the inferoposterior and posterolateral regions (**white arrows**).

asynergy extending over more than one artery region between two observers.

Figure 3 shows a representative example (Case 6) of asynergy within one arterial region. During the attack of spasm associated with ST segment elevation in the inferior leads and ST segment depression in the anterior leads, marked reduction of motion and systolic thickening of the posterior wall is observed with relatively hyperkinetic motion of the septum on the M-mode echocardiogram. No systolic wall thickening is observed in the right coronary artery region during the attack. In this patient, spasm was demonstrated in the right but not the left coronary artery during coronary angiography.

Figure 4 shows a representative example (Case 22) of asynergy extending over more than one arterial region. During the attack of spasm associated with ST segment elevation in the inferior leads and ST segment depression in the anterior leads, motion and systolic thickening of both the posterior wall and the septum were markedly reduced. Systolic wall thickening is observed in neither the right coronary nor the left anterior descending artery region on the two-dimensional echocardiogram during the attack. In this patient, spasm was demonstrated in both the right and the left coronary artery during coronary angiography.

Of the nine patients who exhibited asynergy extending over more than one arterial region, four showed ST segment elevation in the inferior leads with ST depression in the anterolateral leads, three showed ST elevation in the anterior leads with ST depression in the inferior leads and two had simultaneous ST elevation in both the anterior and the inferior leads during the attack of spasm induced by hyperventilation (Table 1).

Seven of the nine patients with asynergy extending over more than one arterial region had spasm demonstrated in both the right and the left coronary artery during the attack in the catheterization laboratory (Fig. 5). In one patient (Case 20), acetylcholine was not injected into the left coronary artery because nitroglycerin was administered after

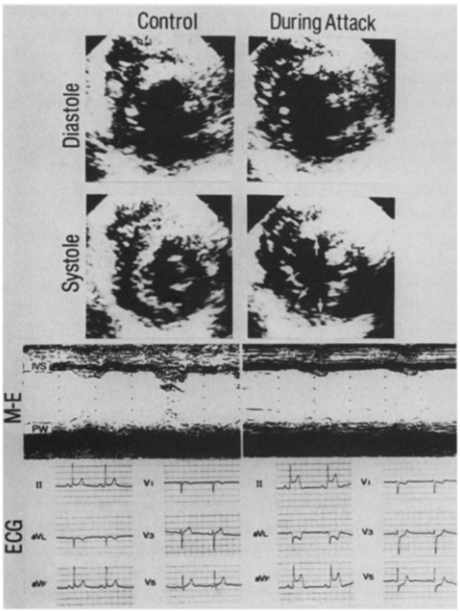

Figure 4. Case 22. Two-dimensional echocardiograms, M-mode (M-E) echocardiograms and electrocardiograms (ECG) in a patient who showed asynergy over more than one coronary artery region. During the attack, the ECG showed the same changes as in Figure 3 whereas reduction of motion and thickening occurred not only in the posterior wall (PW) but also in the interventricular septum (IVS), as shown by the M-mode echocardiogram. The short-axis images of the left ventricle showed absence of systolic wall thickening in the inferior septum to inferoposterior free wall and mid septum (**white arrows**). Abbreviations as in Figure 3

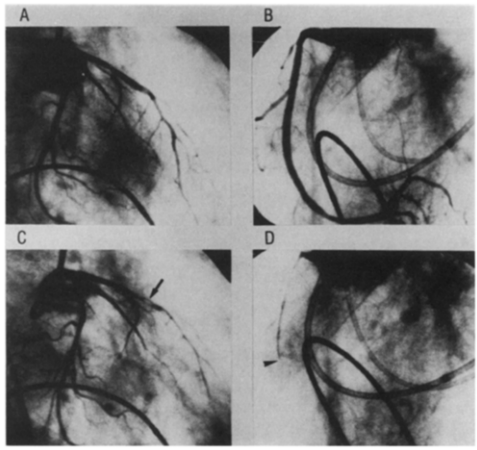

Figure 5. Induction of multivessel coronary spasm by intracoronary injection of acetylcholine. The left (A) and right (B) coronary arteries were normal at baseline. C, Severe vasoconstriction of the left anterior descending artery (**arrow**) with delayed distal filling developed after injection of acetylcholine (50 μg) into the left coronary artery. D, Total occlusion of the right coronary artery (**arrowhead**) occurred after injection of acetylcholine (50 μg) into the right coronary artery.

spasm of the right coronary artery had been demonstrated. In this patient, however, ST segment elevation occurred at times in the anterior leads and at other times in the inferior leads during the spontaneous attack, and thus spasm would be expected to occur in both the right and the left coronary artery. The remaining patient (Case 19) had spasm only in the left anterior descending artery during the attack. However, he had severe organic triple vessel stenosis including a totally obstructed right coronary artery that received collateral vessels from the left anterior descending and left circumflex arteries. Thus, in this patient, spasm of the left anterior descending artery caused asynergy not only in the region of this artery but also in the region of the right coronary artery. Therefore, simultaneous multivessel coronary spasm seems to have occurred in eight of the nine patients who exhibited asynergy extending over more than one arterial region during the attack.

Clinical features of simultaneous multivessel coronary spasm. The clinical, ECG and angiographic findings of the 19 patients with single vessel coronary spasm were compared with those of the eight patients with simultaneous multivessel coronary spasm. The age distribution and gender ratio were similar in both groups. Absence of significant vessel disease (<50% luminal diameter narrowing) was more frequent in the patients with simultaneous multivessel coronary spasm than in those with single vessel coronary spasm (8 of 8 versus 7 of 19, $p < 0.01$). Of the 16 involved coronary arteries in the eight patients with simultaneous multivessel spasm, seven arteries had atherosclerotic changes of 25% luminal diameter narrowing with focal spasm, two had no atherosclerotic changes with focal spasm and the remaining seven had no atherosclerotic changes and diffuse spasm during coronary angiography. During the attack the degree of ST segment elevation was significantly higher in the patients with simultaneous multivessel coronary spasm than in those with single vessel spasm (0.72 ± 0.42 versus 0.37 ± 0.37 mV, mean ± SD, $p < 0.05$). The duration of ST segment elevation was significantly longer in the patients with multivessel than in those with single vessel spasm (260 ± 86 versus 146 ± 64 s, $p < 0.01$), and the incidence of arrhyth-

mias during the attack was significantly higher in the patients with multivessel than in those with single vessel spasm (8 of 8 versus 4 of 19, $p < 0.01$). In addition, all four attacks associated with ventricular tachycardia occurred in patients with simultaneous multivessel coronary spasm.

Discussion

It is now established that variant angina is caused by spasm of a major coronary artery (2–5). In the present study, we used hyperventilation to induce the attack of variant angina. Hyperventilation probably induces coronary spasm by way of respiratory alkalosis because it is known that hydrogen ions compete with calcium ions that are necessary for the contraction of vascular smooth muscle (27,28).

Simultaneous multivessel coronary spasm. There have been scattered reports (7–11) of spasm occurring in more than one major coronary artery (multivessel coronary spasm) in patients with variant angina, but there are no systematic studies on its incidence and clinical features. We recently reported (12) that the incidence rate of multivessel coronary spasm in patients with variant angina is surprisingly high (76%) as judged by examining the susceptibility of each coronary artery to spasm by intracoronary injection of acetylcholine. In the present study, we used two-dimensional echocardiography to examine the wall motion and thickening of the left ventricle during an attack of spasm induced by hyperventilation in 27 patients with variant angina. In all patients, wall motion abnormalities or asynergy of the myocardial area reflected by ST segment elevation on the ECG appeared during the attack and disappeared after nitroglycerin administration. In all but two attacks, ST segment elevation appeared in either the anterior leads, the inferior leads or the lateral leads, suggesting that spasm occurred in one major coronary artery. In two patients (Cases 26 and 27) the attacks were associated with ST segment elevation in both the anterior and the inferior leads, suggesting that spasm occurred in more than one major coronary artery simultaneously. However, the two-dimensional echocardiogram demonstrated that asynergy appeared in more than one coronary artery region in 9 of the 27 patients including the 2 patients with simultaneous ST segment elevation in both anterior and inferior leads. In one of these nine patients (Case 19), the right coronary artery was completely occluded and received rich collateral flow from the left anterior descending and left circumflex arteries; thus it appears that spasm induced in the left anterior descending artery resulted in asynergy of the anterior and inferior regions simultaneously. This result strongly suggests that spasm of more than one major coronary artery or multivessel coronary spasm occurred simultaneously during the attack in the remaining eight patients who manifested asynergy in more than one coronary artery region.

Indeed, coronary angiography demonstrated that spasm was induced in more than one major coronary artery in seven of these eight patients. In the remaining patient (Case 20), spontaneous attacks were associated with ST segment elevation at different times in the anterior and in the inferior leads. In this patient, acetylcholine was not injected into the left coronary artery because nitroglycerin had been administrated after the appearance of spasm in the right coronary artery. We believe, therefore, that simultaneous multivessel coronary spasm occurred in 8 (30%) of our 27 study patients during the attack induced by hyperventilation.

Although spasm of more than one major coronary artery was induced by injecting acetylcholine into the right and the left coronary artery separately in 12 patients and by ergonovine in 2 patients, and although ST segment elevation appeared sometimes in the inferior leads and at other times in the anterior leads during the spontaneous attack in the additional 2 patients, simultaneous multivessel coronary spasm appears to have occurred in 8 of these 16 patients during the attack induced by hyperventilation. This finding may indicate that susceptibility to spasm is different in each coronary artery or that it changes with time, or both, in patients with variant angina.

It has been explained (6) that ST segment depression associated with contralateral ST segment elevation on the ECG during an attack of variant angina indicates electrically reciprocal and not ischemic changes. However, our study shows that six of the eight patients with multivessel spasm had ST segment depression associated with ST segment elevation in the contralateral leads during the attack. Thus, ST segment depression associated with contralateral ST segment elevation during the attack may indicate ischemia and not reciprocal lead changes in some patients with variant angina. Therefore, simultaneous multivessel coronary spasm cannot be diagnosed by ECG alone.

Clinical implications. An attack of simultaneous multivessel coronary spasm was associated with a higher degree and longer duration of ST segment elevation and a higher incidence of arrhythmias, including ventricular tachycardia, than was an attack of single vessel spasm. This finding indicates that simultaneous multivessel coronary spasm is more severe and dangerous than single vessel spasm. It is also to be noted that all eight patients with simultaneous multivessel coronary spasm had no significant organic stenosis on arteriography. There are reports (29,30) showing that the prognosis for patients with variant angina without significant organic stenosis is good. However, there have been reports of patients with normal or almost normal coronary arteries who had simultaneous multivessel coronary spasm that was refractory to sublingual and intravenous nitroglycerin administration and was associated with life-threatening arrhythmias that in some instances resulted in sudden death (31). In our study, the attack of simultaneous multivessel coronary spasm was also serious because the duration of ST segment elevation after sublingual nitroglyc-

erin administration was significantly longer than that in patients with single vessel spasm, and serious arrhythmias such as ventricular tachycardia occurred. Thus, the prognosis for patients with variant angina and no significant organic stenosis is not necessarily good when they have simultaneous multivessel coronary spasm. Indeed, our recent study (32) shows that multivessel coronary spasm is an independent variable affecting the prognosis of patients with variant angina.

Limitations of study. One limitation of the present study was the subjective assessment with use of two-dimensional echocardiography of wall motion abnormalities during the attack, particularly with regard to the hypokinetic segments (21,33). Because the M-mode echocardiogram is more accurate in detecting wall motion changes than is the two-dimensional echocardiogram, we performed the M-mode and two-dimensional echocardiographic examinations simultaneously in all patients (13). Moreover, in contrast to studies of acute myocardial infarction, echocardiograms both before and after subsidence of the attack were available for comparison with those during the attack. Another limitation may be the overestimation of the extent of ischemia in the assessment of wall motion changes because nonischemic muscle can be influenced by adjacent ischemic muscle (22–24). However, recent experimental studies (34) indicate that asynergy is produced only in regions immediately adjacent to an ischemic zone, and a zone of mild hypokinesia extends <1 cm from the ischemic border, whereas the regions beyond that become hyperkinetic. In our study, the region of hypokinesia immediately adjacent to the region of akinesia or dyskinesia was regarded as manifesting adjacent asynergy and not as an ischemic region. Only the segments of asynergy that extended beyond one coronary artery region and were not classified as manifesting adjacent asynergy were regarded as exhibiting remote asynergy due to ischemia of another major coronary artery region. Thus, although there were small discrepancies regarding the exact extent of hypokinesia, there was no discrepancy between two observers with regard to whether asynergy extended over more than one major coronary artery region.

It was easy to determine simultaneous spasm of the left anterior descending artery and the right coronary artery, but it was not easy to determine simultaneous spasm of the right and left circumflex arteries because the regions of these arteries overlap considerably depending on the dominance of the right coronary and the left circumflex artery (21). However, in our series there was only one instance (Case 23) of simultaneous spasm of the right coronary and left circumflex artery and there was no instance of simultaneous multivessel coronary artery spasm of the left anterior descending and the left circumflex artery.

Conclusions. Simultaneous multivessel coronary spasm seems to be induced by hyperventilation in a sizable proportion of patients (30%) with variant angina, particularly those with angiographically normal or nearly normal coronary arteries, and it can be detected by two-dimensional echocardiography. Because an attack of simultaneous multivessel coronary spasm is associated with more severe and more prolonged myocardial ischemia than is an attack of single vessel coronary spasm and is often associated with life-threatening arrhythmias, the patients with this condition should be treated more aggressively and followed up more carefully.

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